

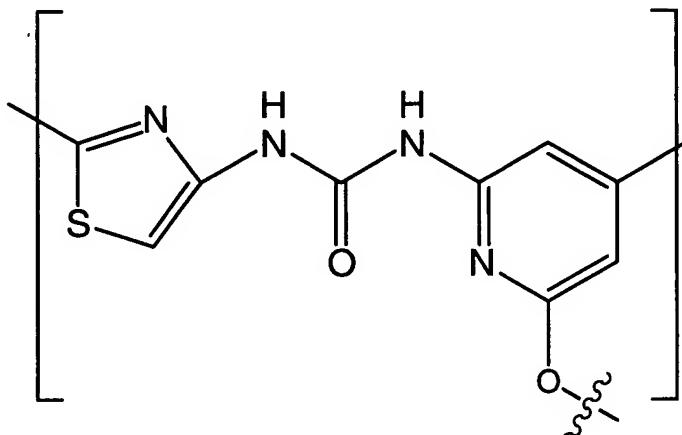
**Remarks**

In response to the Office Action mailed January 25, 2006, applicants submit the preceding amendments and request their entry. Following entry of the amendment, claims 2-12, 14, 67, and 111-134 remain pending, claims 1, 13, 15-66 and 68-110 having been canceled. All pending claims have been amended.

Independent method claims 14, 111, and 123 respectively directed to a method of inhibiting cell proliferation, a method of treating cancer, and a method of inhibiting a serine/threonine kinase are the only pending independent claims.

The specification has been amended simply to correct a mis-numbered example.

The claims have been amended in a manner responsive to the new restriction requirement. As described in more detail below, the claims have been directed to the therapeutic use of compounds with the following core structure:



Independent claims 14, 111 and 123 have been amended to embrace this core structure and to ensure that the amended claims embrace the specifically described compounds that possess this core structure. All of the dependent claims have been amended consistent with the scope of the amended independent claim from which they depend.

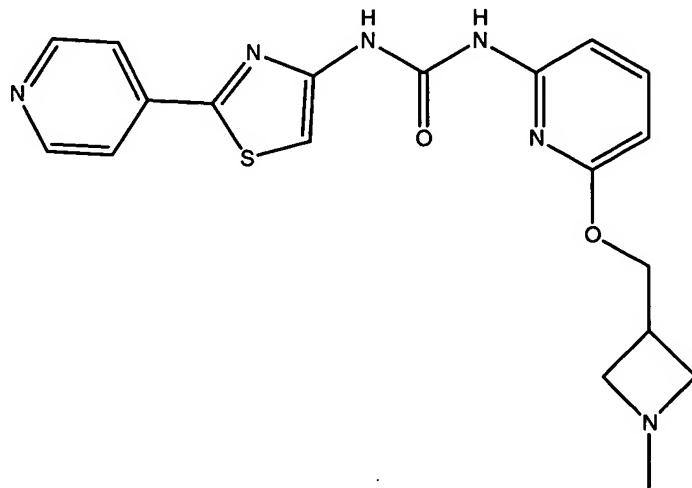
The Office Action unfairly treats applicants' prior response as a response to a restriction requirement, indicating that all of the pending claims "(all claims in part) are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention."

Applicants strenuously object to this treatment.

The prior Office Action was NOT presented as a restriction requirement. The Office Action deferred any restriction asking applicants simply to make an election of species. Specifically, the Office Action noted “upon election of a single compound, the Office will review the claims and disclosure to determine the scope of the independent invention encompassing the elected compound (compounds which are so similar thereto as to be within the same inventive concept and reduction to practice).” From that election, applicants anticipated that this next Office Action would present the “restricted invention” with an invitation for applicants to traverse the requirement. Pointedly, the prior Office Action specifically noted “Note that the restriction requirement will not be made final until such time as applicant is informed of the full scope of compounds along with (if appropriate) the process of using or making said compound under examination.” (Emphasis added)

Indeed, the prior Office Action did not define or identify even a single independent and distinct invention. Thus, applicants were never given the opportunity to traverse the restriction requirement that is, for the first time, made in the current Office Action. Applicants take that opportunity at this time.

As noted in the Office Action, applicants elected the compound



1-[6-(1-Methyl-azetidin-3-ylmethoxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

A key feature of this compound is the ether linkage on the core pyridyl as shown earlier. This feature is possessed by a number of specifically described compounds as shown in Examples 93, 94, 102, 104, 107-114, 263-270, 272-275, 284, 285, 288, 289, 300, 301, 304, 305, 312-314, 315, 316, 319-321 and 326-342. Applicants submit that the proposed restriction

requirement limiting the moiety linked through the ether oxygen to solely “an optionally substituted heterocycl C<sub>1</sub>-C<sub>4</sub> alkoxy group” is unnecessarily limited and is not warranted by either a specific classification requirement or because not to do so would unreasonably enlarge the scope of any searching. Applicants thus contend that the restriction requirement should be modified to enlarge the definition of R<sup>15</sup> to embrace not only such optionally substituted heterocycl C<sub>1</sub>-C<sub>4</sub> alkoxy group, but also an optionally substituted heterocycloxy, a C<sub>1</sub>-C<sub>4</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy, and an optionally substituted phenoxy.

Moiety R<sup>16</sup> has been limited in the manner imposed by the proffered restriction requirement.

Moiety R<sup>17</sup> also has been limited but in a manner that departs somewhat from that imposed by the proffered restriction requirement. In particular, R<sup>17</sup> has been limited in a way to eliminate compounds not represented by Examples 93, 94, 102, 104, 107-114, 263-270, 272-275, 284, 285, 288, 289, 300, 301, 304, 305, 312-314, 315, 316, 319-321 and 326-342. Applicants submit that they are entitled to a claim embracing the compounds specifically illustrated by the pending application and linked by the noted common core structure.

As regards the proffered restriction, applicants have amended the claims to embrace a common core feature that distinguishes the claims from other compounds considered by the Office Action as being independent and distinct and request reconsideration and allowance of the claims as presented.

The claims were objected to for containing non-elected subject matter (page 6 of Office Action), indicating that “[c]laims drawn solely to the elected invention as identified *supra* would appear allowable.” Applicants submit that the claims have been amended in a way that is consistent with a suitable restriction and offer them for consideration of their allowability.

On page 4 of the Office Action claims were rejected under 35 USC 112, first paragraph, as not being enabled. Applicants submit that with the foregoing amendments this rejection is not sustainable.

As noted above, the three independent claims 14, 111, and 123 are respectively directed to a method of inhibiting cell proliferation, a method of treating cancer, and a method of inhibiting a serine/threonine kinase.

Cell proliferation is the rapid reproduction of cells, such as by cell division. The cell cycle, which controls cell proliferation, is itself controlled by a family of serine-threonine kinases called cyclin dependent kinases (CDKs). The regulation of CDK activation is complex, and

requires the association of the CDK with a member of the cyclin family of regulatory subunits. A further level of regulation occurs through both activating and inactivating phosphorylations of the CDK subunit. The coordinate activation and inactivation of different cyclin/CDK complexes is necessary for normal progression through the cell cycle. Both the critical G1-S and G2-M transitions are controlled by the activation of different cyclin/CDK activities. Loss of control of CDK regulation is a frequent event in hyperproliferative diseases and especially cancer. (T. Noguchi et al., Am. J. Pathol., 156, 2135-47 (2000)) As such, inhibition of CDKs has become an important target in the study of chemotherapeutics for chemical entities useful for treating cell proliferation diseases, including cancer. (A. Senderowicz and E. Sausville, J. Nat. Canc. Inst., 92, 376-87 (2000))

Protein kinases also control programmed cell death, also known as apoptosis. Apoptosis is a ubiquitous physiological process used to eliminate damaged or unwanted cells in multicellular organisms. Disregulation of apoptosis is believed to be involved in the pathogenesis of many human diseases, including cancer. The failure of apoptotic cell death has been implicated in various cancers, as well as autoimmune disorders. Conversely, increased apoptosis is associated with a variety of diseases involving cell loss such as neurodegenerative disorders and AIDS. As such, inhibition of apoptosis has become an important therapeutic target. Cdk5 in particular has been shown to be involved in apoptosis pathology (A. Catania et al., Neuro-Oncology, 89-98 (April 2001)).

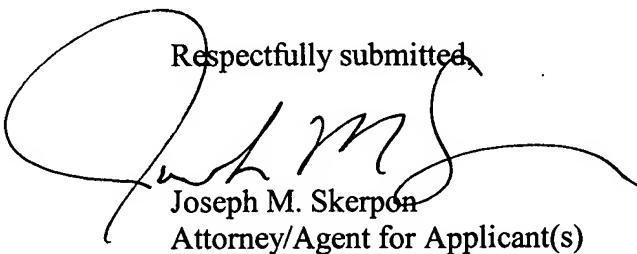
Examples 263-268, 270, 273-275, 288, 300, 301, 304, 316, 319-321, 327-330, 332-335, 337-338, and 340-342, all falling within the scope of the amended claims have exhibited cdk2/cyclin kinase activity with  $IC_{50}$  values less than 0.5  $\mu$ M. The compounds of examples 263-268, 273-275, 288, 300, 301, 304, 313, 315, 316, 319-321, 328-330, 332-335, 337-338, and 340-342, which also all fall within the scope of the amended claims also exhibited cdk5/p25 kinase activity with  $IC_{50}$  values less than 0.5  $\mu$ M. Applicants submit that these experimental results support the proffered amended method claims under 35 USC 112.

On the basis of the foregoing amendments and the accompanying remarks, the pending claims now are in condition for allowance. Applicants respectfully request the reconsideration and full allowance of the pending claims.

If any fees need to be paid to enter this amendment, the Commissioner is hereby authorized to charge any additional filing fees which may be required to Deposit Account No. 19-0733.

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Respectfully submitted,



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